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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,687	11/15/2001	Matthew C. Coffey	032775-078	7186

26181 7590 07/26/2005

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,687	COFFEY ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *attached* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 5/9/2005. The amendment filed 5/9/2005 is acknowledged. The amendment has been entered. Claims 14, and 17-21 have been cancelled. Claims 1-13, 15 and 16 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO 99/08692, previously cited). In view of Heise et al. (Cancer Gene Therapy, 11/1/99; cited in IDS filed 3/2004), for the reasons of record set forth in the Office Action mailed 12/10/2004, which are reiterated below.

Lee teaches a method for directly delivering an oncolytic reovirus serotype 3 Daring strain virus (which is a human serotype 3 reovirus) by injection into a solid tumor to reduce growth of the tumor. Lee teaches that the method comprises administering an effective amount of virus to a subject bearing the tumor, wherein the virus is capable of selectively replicating in and killing tumor cells and wherein the virus is administered in a single dose or in multiple doses (i.e. more than one does) and the multiple doses can be administered concurrently (at the same time) or consecutively (i.e. either before or after the base administration). (See, for instance, abstract; p.3 lines 1-15; p.9, lines 17-20; p.34, lines 9-17; Examples 9 and 10; and Claim 38). Lee also teaches a tumor treatment wherein a tumor that has an area of with a mean area of $0.31cm^2$ are treated with an injection of oncolytic virus (see page 27, last paragraph). Using the following formulas, AREA=$4\pi(r)^2$ and VOLUME=$(4/3)\ \pi(r)^3$, the volume of the tumors was calculated to be about $0.17cm^3$. Therefore, Lee teaches an injection of oncolytic virus per $0.25cm^3$ of the tumor.

As such, Lee teaches a method of injecting a reovirus into a solid tumor (e.g., see claim 27) comprising multiple doses (i.e., multiple injections) which are administered concurrently (i.e., on the same day). Lee teaches that the method can comprise the additional administration

of the therapeutic virus by other routes of administration, including systemic administration of human reovirus; or topically or by spray (e.g., see page 9). It is noted that multiple administrations encompasses more than one administration.

Lee does not explicitly teach the volume of the viral composition that is injected into the tumor or the exact number of times that the viral composition is injected into the tumor, nor does Lee teach that the oncolytic virus that is administered is a modified adenovirus, such as ONYX-015.

However, Heise teaches the importance of virus distribution when using an oncolytic virus to treat a tumor. Specifically, Heise teaches,

> "These data suggested that replication-dependent tumor cell lysis and spread was occurring, but that tumor destruction might be improved by increasing i.t. (intratumoral) virus distribution. Two treatment parameters were then varied to determine whether virus distribution, and consequently efficacy, could be improved. Divided i.t. injections of virus were more efficacious than a single injection of the same total dose. Likewise, increasing the volume of the viral suspension for i.t. injection allowed better distribution within the tumor mass and increased efficacy. These results have implications for the treatment of cancer patients with viral agents.

Clearly indicating that the when treating a cancer patient with a viral agent such as an oncolytic virus, increasing the distribution of the virus in the tumor, such as by injecting the virus multiple time or injecting a larger volume of virus solution, will increase the efficacy of the treatment. Furthermore, Heise teaches that the oncolytic virus ONYX-015 (which is a modified adenoviral vector) is injected into a C33a tumor that is ~200mm^3 wherein the virus is administered in a total volume of 100ul, which is 50% of the volume of the tumor (e.g., see p. 500, second column, second paragraph under "Effects of virus suspension volume on efficacy and i.t. distribution."). It is noted that the reovirus used by Lee and the ONYX-015 virus used by Heise are both oncolytic viruses that have can be used for tumor treatment.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the method taught by Lee to make a method for delivering a virus to a solid tumor by administering on the same day a composition comprising either an oncolytic Dearing strain reovirus or an oncolytic ONYC-015 virus, wherein the volume of the virus composition is between about 10% and about 100% of the tumor volume (and at least 50% of the tumor volume), wherein the virus is delivered to multiple sites in the tumor, wherein the virus is administered by injection into one site per about 0.25 cc of the tumor, and wherein the method further comprises at least one additional administration of a Dearing strain virus by systemic administration, or topical/transdermal patch/spray on the skin when the tumor is a superficial tumor with a reasonable expectation of success.

The motivation to make such a modification is supplied by Heise who specifically teaches that increasing the distribution of an oncolytic virus solution in a tumor, by means such as using multiple injections or increasing the volume of the oncolytic viral solution that is administered can increase the efficacy of the treatment.

It would further have been prima facie obvious to perform routine optimization to determine the most effective number of administrations or the exact volume of viral composition administered. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the injecting an oncolytic viral composition to multiple sites in a tumor the same day wherein the number of sites injected is at least 3 sites or at least 5 sites inside the tumor results in an

unexpected result in view of the closest prior art. The closest prior art being (1) Heise, which teaches increasing the distribution of an oncolytic virus composition in a tumor (by using multiple injections or adjusting the volume of the composition that is administered) increases the efficacy of the treatment, and (2) Lee, which teaches treating tumors by administering an oncolytic virus in multiple doses wherein the doses can be administered concurrently (i.e., on the same day).

Response to Arguments

Applicant's arguments filed 5/9/2005 have been fully considered but they are not persuasive.

Applicants argue that a skilled artisan would not have been motivated by the cited references to combine the base administration with the additional administration of the claimed invention. Applicants assert that with respect to the mode of delivery, Lee et al. teach that for a solid neoplasm that is accessible, the reovirus can be injected directly into the neoplasm (page 8); for neoplasms that are not easily accessible within the body, such as metastases or brain tumors, the reovirus can be administered systemically (pages 8-9). Applicants also assert that Lee et al. further teach that "[A]lternatively, the reovirus can be administered directly to a single solid neoplasm, where it then is carried systemically through the body to metastases" (page 9). Applicants contend that Lee et al. does not specifically teach or suggest the desirability of combining intratumor injections and systemic delivery. With respect to Heise et al., Applicants argue that Heise et al. also do not teach or suggest combining intratumor injections and systemic delivery; and contend that neither reference teaches or suggests the combination of intratumor

injections and a transdermal patch/ spray on the skin/topical administration as recited in claim 1. Therefore, Applicants argue, there is no suggestion or motivation to modify the teachings of the cited references, either alone or in combination, to arrive at the claimed invention (e.g., see pages 6-8 of the communication filed 5/9/2005).

In response, Applicants arguments have been fully considered, but are not persuasive. Upon closer evaluation of the WO 99/08692 reference, it is clear that the reference does contemplate different routes of administration, multiple doses, and treating more than one neoplasm in a subject. Specifically, the WO 99/08692 reference teaches:

> "The reovirus can be administered in a single dose or in multiple doses; furthermore, more than one neoplasm in an individual mammal can be treated concurrently. Both solid neoplasms and hematopoietic neoplasms can be targeted. The reovirus is administered so that it contacts cells of the mammal (e.g., by injection directly into a solid neoplasm, or intravenously into the mammal for a hematopoietic neoplasm)." (See p. 3, first pragrah);
>
> "A wide variety of administrations can be employeed. For example, for a solid neoplasm that is accessible, the reovirus can be administered by injection directly to the neoplasm. For a hematopoietic neoplasm, for example, the reovirus can be administered intravenously or intravascularly. For neoplasms that are not easily accessible within the body, such as metastases or brain tumors, the reovirus is administered in a manner such that it can be transported systemically through the body of the mammal and thereby reach the neoplasm." (See p. 8, last paragraph).
>
> "Alternatively, the reovirus can be administered directly to a single solid neoplasm, where it then is carried systemically through the body to metastases." (See p. 9, first paragraph).

It is noted that direct administration to a solid neoplasm where it is then carried systemically through the body to metastases is a clear teaching of direct delivery and further systemic delivery of the therapeutic virus.

Furthermore, the WO 99/08692 reference clearly teaches treating multiple neoplasms in a mammal. The reference teaches treating solid neoplasms by direct delivery and treating

metastases by systemic delivery (see above). Therefore, the reference does teach multiple routes of administration including direct intratumoral delivery and systemic delivery. The reference also provides motivation for the combination of direct intratumoral delivery and systemic delivery: for treating multiple neoplasms in a mammal such as solid tumors and metastases. Therefore, Applicants arguments are not persuasive and the rejection is not withdrawn.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Anne-Marie Falk
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